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Review Article

## The era of pharmacovigilance and the need of pharmacovigilance in psychiatry: A review

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### ABSTRACT

According to WHO, Adverse drug reaction (ADR) is defined as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function”. Adverse drug reactions occur almost daily in every health care institution and can adversely affect a patient’s quality of life (QOL), often causing considerable morbidity and mortality. With the setting up of the Pharmacovigilance Program in India, it is important for all psychiatrists, pharmacist and nurses to familiarize themselves with the key principles of this science, and to apply the principle of Pharmacovigilance for the welfare of our patients and the entire health care community.

**Keywords:** Adverse drug reaction (ADR), prophylaxis, diagnosis, patient’s quality of life (QOL)

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### Introduction

According to WHO, Adverse drug reaction(ADR) is defined as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function”.An adverse drug reaction (ADR) is an unwanted, undesirable effect of a medication that occurs during usual clinical use.<sup>1</sup> Adverse drug reactions occur almost daily in every health care institutions and can adversely affect a patient’s quality of life (QOL), often causing considerable morbidity and mortality. Serious attention has been given to identifying the patient populations most at risk, the drugs most commonly responsible, and the potential causes of ADRs. It is mainly due to an an increase in the number of drugs on the market, an aging population, and a trend of poly-pharmacy. Adverse drug reactions may cause patients to lose their confidence ,negative emotions toward their healthcare profession & institution and seek self-medication practice, which may results in additional ADRs.<sup>2</sup> With 10% of 3.63 trillion medicines popped worldwide in 2015, India is the world’s third-largest medicine market. It stands to scientific reason

that these drugs will have side effects. Yet, in 2013, India reported no more than 2% of globally occurring adverse drug reactions; jargon for side effects of medicines, logged in a database maintained by the Uppsala Monitoring Centre .It isn’t as if drugs have fewer side effects in India. Serious effects were seen in 6.7% of patients, a 2014 study reported. Other studies have cited drug side effects as the reason for 3.4% of hospital admissions in India, 3.7% hospital re-admissions, and 1.8% mortality. In the developed world, adverse reactions are believed to be the fourth-leading cause of death. Within India, the adverse drug reaction reporting rate (ADRs reported per million population) has almost doubled in the last three years to 40, but it is lower than 130, the average ADR reporting rate for high-income countries, and clearly disproportionate to the country’s population and medicine consumption.<sup>3</sup>

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. WHO established its Programme for International Drug Monitoring in response to the thalidomide disaster detected in 1961. Together with the

WHO Collaborating Centre for International Drug Monitoring, Uppsala, WHO promotes PV at the country level. At the end of 2010, 134 countries were part of the WHO PV Programme. The aims of PV are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines.<sup>4</sup>

### Evolution of Pharmacovigilance

The birth of Pharmacovigilance has a close relationship to psychiatry. Thalidomide was first synthesized in 1953 and became popular as a sedative prescribed for the morning sickness associated with pregnancy. By 1958, thalidomide was being advertised and promoted around the world. In April 1961, obstetrician William McBride began to notice cases of a rare birth defect, Phocomelia in babies whose mothers had used thalidomide in pregnancy. At the Crown St. Women's Hospital in Sydney, Australia, where McBride practiced, he soon persuaded the hospital to stop using the drug and wrote of his concerns to Distillers, the company that sold the drug in Australia. At about the same time, pediatrician and geneticist Widukind Lenz noted many similar cases in Germany, where thalidomide was available without prescription. At this time, physicians assumed that the placenta was impervious to any drugs the expectant mother ingested—unless the drug actually killed her. This belief persisted despite experimental evidence to the contrary. Since thalidomide was not fatal in overdose, it was deemed safe. When thalidomide was approved, drugs were not tested in pregnant animals for their teratogenic effect—that is, for their ability to cause developmental abnormalities in the fetus. McBride wrote the letter below to a leading medical journal, *The Lancet*, to alert the medical community to the dangers of thalidomide, from that moment the era of Pharmacovigilance was started.<sup>5, 6-13</sup>

### Chronological Development of Pharmacovigilance

1747: James Ling reported clinical trial showing effectiveness of lemon juice in prevention of scurvy.

1937: Sulphanilamide disaster, where sulphonamide was dissolved in diethyleneglycol leading to death of more than 100 people because of renal failure.

1938: The preclinical toxicity and pre-marketing clinical studies made mandatory by FDA.

1950s: Aplastic anaemia caused due to use of chloramphenicol.

1960: The FDA started hospital based drug monitoring program.

1961: Thalidomide disaster.

1963: 16<sup>th</sup> world health assembly recognized importance to rapid action on ADR.

1968: Establishment of International Drug Monitoring Program by WHO.

1970s: Clioquinol was found to be linked with Sub-acute-myelo-optic neuropathy.

1980s and 1990s: Many drugs with serious adverse effects were recorded.

1996: India started global standard clinical trial.

1997: India joined ADR Monitoring Program.

1998: PV activity initiated in India.

2002: 67<sup>th</sup> National Pharmacovigilance Centre established in India.

2005: India started conducting structured clinical trials.

2009-2010: PV plan of India was initiated and implemented.

15th April 2011: The NCC was transferred from AIIMS, New Delhi to IPC, and Ghaziabad for smooth and efficient functioning of program.

Till January 2017: 250 AMCs (government and non-government) have been established under PvPI.<sup>7</sup>

The discipline of Pharmacovigilance is of particular importance in the field of psychiatry. Pharmacotherapy is the principal modality of management in several psychiatric disorders and psychotropic drugs are associated with a variety of adverse drug reactions. Over the past decades, Pharmacovigilance activity has led to the identification of several adverse drug reactions caused by psychotropic drugs, resulting in their withdrawal from the market or restrictions in use. Psychotropic medications are often administered for longer periods and are commonly prescribed in combination with other drugs and, therefore, may be involved in clinically relevant drug interactions. Psychotropic agents may be prescribed to populations at higher risk of developing adverse effects. In particular, they are increasingly used to treat psychiatric disorders in children and adolescents, as well as in the elderly, and may be used by pregnant or lactating women. The main source of knowledge on tolerability and safety of psychotropic drugs comes from clinical trials, but this is associated with several limitations. Pharmacovigilance programs are designed to gather information on what effects drugs have in the real world rather than in groups of carefully selected clinical trial populations. For the above mentioned reasons, it is important that psychiatrists become familiar with the concepts and methods of pharmacovigilance as they have a key role in identifying and reporting new or serious adverse drug effects.<sup>4</sup>

### Four reasons why this field is of special importance to psychiatrists.

**First**, often, patients do not respond to initial drug therapy, and may require several trials of different medications. Some patients may require a combination of various drugs which can increase the risk of adverse effects or drug interactions.

**Second**, most clinical trials of psychotropics are conducted in "ideal" conditions patients are selected according to stringent criteria, and comorbid medical conditions are usually excluded. These trials also tend to be short-term, lasting for a few weeks or months. In this context, ADRs that were not noticed in the context of a trial become more apparent, and the burden of managing them falls on the psychiatrist.

**Third**, there is a publication bias in clinical trials, particularly those in psychiatry. Even in published trials, ADRs are not always reliably reported, and there is a concern that relevant data may be misrepresented in some cases.<sup>11</sup> Hence, the onus is on treating psychiatrists to identify such reactions and report them, particularly those related to newer drugs.

**Fourth**, psychotropics directly affect brain functioning, and can produce undesirable changes in behavior. Sometimes, these changes can be life-threatening, as in the case of suicidal behavior induced by antidepressants in children.<sup>12</sup>

## The benefits of pharmacovigilance in a psychiatric setting

The positive effects of pharmacovigilance in psychiatry can be broadly divided into four categories: Benefits to the patient, benefits to clinicians, benefits to the pharmaceutical industry, and benefits to regulatory authorities.

1. Benefits to the patient: Most adverse drug events, even if not life-threatening, can be distressing and troublesome to patients. Reporting these events could help in building trust between patients and physicians. The practice of regular reporting can also lead to earlier identification of problems, which can improve patient compliance and quality of life.

2. Benefits to the physician: The practice of pharmacovigilance can help psychiatrists to identify and manage potential ADRs. In several cases, physicians may be responsible for bringing a particular ADR to light, and can gain credit for this. This is particularly the case for events such as behavioral toxicity (drug-induced mania,

drug-induced suicidality) that are best recognized by practitioners who are in close contact with their patients.

3. Benefits to the pharmaceutical industry: The role of the pharmaceutical industry in psychiatry has come under fire recently, with reports of serious ADRs being under-reported and suppressed during trials. If the principal investigators in such trials develop a "culture of pharmacovigilance," then such ADRs can be identified at the earliest possible stage, and necessary action taken before the drug is marketed. The CDSCO has made the reporting of adverse reactions by the pharmaceutical industry mandatory. This is known as "periodic safety update reporting" (PSUR).<sup>14</sup>

4. Benefits to regulatory authorities: As mentioned above, most published trials of psychotropic medication are short-term trials. Regulatory authorities may grant approval on the basis of this data, but long-term adverse effects may emerge much later. Early "signal detection" of such events could help authorities in withdrawing the drug responsible, or limiting its use.<sup>9</sup>

## Reporting of adverse drug reaction

<b>What to report?</b>	Life-threatening event or death Hospitalization of the patient Congenital anomaly Medically significant event (If the event is considered serious by physician) Lack of efficacy connected with the use of a medical device or drug product. All suspected drug interactions All known or unknown, serious, non-serious, frequent or rare reaction caused due to use of vaccine or drug must be reported.
<b>When to report?</b>	All spontaneous case should be reported within 10 days. All suspected ADR should be reported as soon as possible because over reporting is always better than under reporting. Death event must be reported as soon as possible, while all other serious ADR/event needs to report within 7 days only. All non-serious cases must be reported within 30 days
<b>Who can report?</b>	Professionals working in healthcare team are the preferred source of information in PV, for example Medical specialists Pharmacists Dentists Midwives Along with HCPs patient, patient's relatives, witness or any common person after medical confirmation can report.
<b>How to report?</b>	Duly filled ADR reporting form needs to send to the nearest AMC or directly to the NCC. Dial toll free helpline number-1800 180 3024 to report ADRs. Mailing the filled ADR reporting form directly to pvpi@ipcindia.net or pvpi.ipcindia@gmail.com. Logging on to the <a href="http://www.ipc.gov.in">http://www.ipc.gov.in</a> , <a href="http://www.ipc.gov.in/PvPI/pv_home.html">http://www.ipc.gov.in/PvPI/pv_home.html</a> for list of authorized AMCs of India
<b>Where to report?</b>	Various Peripheral, Regional and Zonal centres have been proposed and established in India . <b>Peripheral PV centre:</b> It is a primary ADR information gathering centre. It includes small medical centres, private hospitals, dispensaries, nursing home and pharmacies. ADRs are recognized and synchronized by RPCs or ZPCs. Every state, Union territory and few leading medical colleges in India have this peripheral centre. <b>Regional PV centre:</b> It's regarded as secondary PV Centre. It is located in medical college having relatively larger facilities. They are identified and coordinated by zonal centres. There are five such regional centres in India. <b>Zonal PV centres:</b> It's regarded as Tertiary PV Centre. Generally located in metro city's medical college having attachment of sufficient facility. It is identified by CDSCO and act as first ADR data collection centre. Zonal centre for North and East zone is AIIMS.

## Conclusion

Pharmacovigilance is an essential activity for all health care professional. In the field of psychiatry, where long-term drug therapy is the norm, clinicians are ideally placed to identify and report ADRs to regulatory authorities. With the setting up of the Pharmacovigilance Program in India, it is important

for all psychiatrists, pharmacist and nurses to familiarize themselves with the key principles of this science, and to apply the principle of pharmacovigilance for the welfare of our patients and the entire health care community.

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